Charles M. Lizza
William C. Baton
SAUL EWING LLP
One Riverfront Plaza, Suite 1520
Newark, NJ 07102-5426
(973) 286-6700

Attorneys for Plaintiffs
Helsinn Healthcare S.A. and
Roche Palo Alto LLC

Of Counsel:

Joseph M. O'Malley, Jr.
Bruce M. Wexler
Eric W. Dittmann
David M. Conca
Gary Ji
Angela C. Ni
PAUL HASTINGS LLP
75 East 55th Street
New York, NY 10022
(212) 318-6000

Attorneys for Plaintiff
Helsinn Healthcare S.A.

Mark E. Waddell
LOEB & LOEB LLP
345 Park Avenue
New York, NY 10154
(212) 407-4127

Attorneys for Plaintiff
Roche Palo Alto LLC

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

HELSINN HEALTHCARE S.A. and ROCHE PALO ALTO LLC, Plaintiffs, v. DR. REDDY'S LABORATORIES, LTD., DR. REDDY'S LABORATORIES, INC., SANDOZ INC., TEVA PHARMACEUTICALS USA, INC., and TEVA PHARMACEUTICAL INDUSTRIES, INC., Defendants.	Civil Action No. 13-5815 (MLC) (DEA) Civil Action No. 11-3962 (MLC) (DEA) (Consolidated) Hon. Mary L. Cooper, U.S.D.J. Hon. Douglas E. Arpert, U.S.M.J. (Filed Electronically)

DECLARATION OF ANGELA C. NI IN SUPPORT OF
PLAINTIFFS' OPENING CLAIM CONSTRUCTION BRIEF

I, Angela C. Ni, declare under penalty and perjury that:

1. I am a member of the bars of the States of New York and New Jersey, and am admitted to practice before this Court, the Court of Appeals for the Federal Circuit, and the Southern and Eastern Districts of New York. I am an associate at the law firm of Paul Hastings LLP, 75 East 55th Street, New York, New York 10022, counsel for Plaintiff Helsinn Healthcare S.A. in this matter.

2. I submit this declaration in support of Helsinn Healthcare S.A. and Roche Palo Alto LLC's (collectively, "Plaintiffs'") Opening Claim Construction Brief, submitted herewith.

3. Attached as Exhibit 1 hereto is a true and correct copy of United States Patent No. 8,598,219 ("the '219 patent").

4. Attached as Exhibit 2 hereto is a true and correct copy of Defendants' Proposed Claim Terms for Construction, dated May 5, 2014, that was submitted in consolidated Civil Action No. 11-3962/13-5815 (MLC)(DEA) ("the current action").

5. Attached as Exhibit 3 hereto is a true and correct copy of Defendants' Preliminary Claim Constructions, dated May 12, 2014, that was submitted in the current action.

6. Attached as Exhibit 4 hereto is a true and correct copy of Defendants' June 9, 2014 e-mail to Plaintiffs, including Defendants' redline attachment.

7. Attached as Exhibit 5 hereto is a true and correct copy of an Aloxi® label, bearing bates number HELSN0117262-69.

8. Attached as Exhibit 6 hereto is a true and correct copy of the article, J. Laszlo, *Nausea and Vomiting as Major Complications of Cancer Chemotherapy*, 25 (Suppl. 1) Drugs, 1-7 (1983).

9. Attached as Exhibit 7 hereto is a true and correct copy of portions of the redacted Expert Report of Lee Kirsch, Ph.D., dated September 9, 2013, which was cited during the prosecution of the '219 patent, bearing bates numbers HELSN03971578, -188, -189, and -220.

10. Attached as Exhibit 8 hereto is a true and correct copy of an Amendment and Response to Office Action Concerning U.S. Patent Application No. 11/388,269 ("the '269 application"), dated January 9, 2009.

11. Attached as Exhibit 9 hereto is a true and correct copy of an Office Action from the prosecution history of U.S. Patent No. 7,947,724 ("the '724 patent"), dated October 6, 2008, bearing bates numbers HELSN0001623-32.

12. Attached as Exhibit 10 hereto is a true and correct copy of an Amendment and Response to Office Action from the prosecution history of the '724 patent, dated April 6, 2009, bearing bates numbers HELSN0001654-67.

13. Attached as Exhibit 11 hereto is a true and correct copy of an Amendment After Final from the prosecution history of U.S. Patent No. 7,960,424 ("the '424 patent"), dated December 29, 2008, bearing bates numbers HELSN0000324-35.

14. Attached as Exhibit 12 hereto is a true and correct copy of an Office Action from the prosecution history of the '424 patent, dated October 29, 2008, bearing bates numbers HELSN0000313-21.

15. Attached as Exhibit 13 hereto is a true and correct copy of an Appeal Brief from the prosecution history of the '724 patent, dated May 24, 2010, bearing bates numbers HELSN0002129-50.

16. Attached as Exhibit 14 hereto is a true and correct copy of a Notice of Allowance and Fee(s) Due from the prosecution history of the '724 patent, dated March 4, 2011, bearing bates numbers HELSN0002287-89.

17. Attached as Exhibit 15 hereto is a true and correct copy of an Office Action from the prosecution history of U.S. Patent No. 7,947,725 ("the '725 patent"), dated March 29, 2010 bearing bates numbers HELSN0003209-21.

18. Attached as Exhibit 16 hereto is a true and correct copy of an Appeal Brief from the prosecution history of the '725 patent, dated October 11, 2010, bearing bates numbers HELSN0003242-74.

19. Attached as Exhibit 17 hereto is a true and correct copy of a Notice of Allowance and Fee(s) Due from the prosecution history of the '725 patent, dated December 22, 2010, bearing bates numbers HELSN0003471-3.

20. Attached as Exhibit 18 hereto is a true and correct copy of an Appeal Brief from the prosecution history of the '424 patent, dated November 13, 2009, bearing bates numbers HELSN0000413-35.

21. Attached as Exhibit 19 hereto is a true and correct copy of a Notice of Allowance and Fee(s) Due from the prosecution history of the '424 patent, dated January 26, 2010, bearing bates numbers HELSN0000498-500.

22. Attached as Exhibit 20 hereto is a true and correct copy of Defendants' Preliminary Claim Constructions, dated March 6, 2012, that was submitted in the current action.

23. Attached as Exhibit 21 hereto is a true and correct copy of portions of the redacted Expert Report of Patrick P. DeLuca, Ph.D., dated September 9, 2013, which was cited

during the prosecution of the '219 patent, bearing bates numbers HELSN0397112, -117, -118, and -157.

24. Attached as Exhibit 22 hereto is a true and correct copy of portions of Sandoz Inc.'s Invalidity Contentions Pursuant to L. Pat. R.3.6(c), dated December 1, 2011, which was cited during the prosecution of the '219 patent.

25. Attached as Exhibit 23 hereto is a true and correct copy of an Office Action from the prosecution history of the '724 patent, dated August 30, 2006, bearing bates numbers HELSN0001465-73.

26. Attached as Exhibit 24 hereto is a true and correct copy of an Amendment and Response Submitted Under 37 C.F.R. § 1.111 from the prosecution history '724 patent, dated February 26, 2007, bearing bates numbers HELSN0001484-87.

27. Attached as Exhibit 25 hereto is a true and correct copy of an Office Action from the prosecution history of the '725 patent, dated July 17, 2006, bearing bates numbers HELSN0002458-65.

28. Attached as Exhibit 26 hereto is a true and correct copy of an Amendment and Response Submitted Under 37 C.F.R. § 1.111 from the prosecution history of the '725 patent, dated July 28, 2006, bearing bates numbers HELSN0002468-76.

29. Attached as Exhibit 27 hereto is a true and correct copy of an Office Action from the prosecution history of the '424 patent, dated July 13, 2006, bearing bates numbers HELSN0000080-87.

30. Attached as Exhibit 28 hereto is a true and correct copy of an Amendment and Response Submitted Under 37 C.F.R. § 1.111 from the prosecution history of the '424 patent, dated July 28, 2006, bearing bates numbers HELSN0000093-99.

31. Attached as Exhibit 29 hereto is a true and correct copy of an Office Action from the prosecution history of the '269 application, dated July 19, 2006.

32. Attached as Exhibit 30 hereto is a true and correct of an Amendment and Response Submitted Under 37 C.F.R. § 1.111 from the prosecution history of the '269 application, dated July 28, 2006.

33. Attached as Exhibit 31 hereto is a true and correct copy of an Office Action from the prosecution history of the '219 patent, dated July 29, 2013, bearing bates numbers HELSN0396855-66.

Executed this 19th day of June, 2014, at New York, New York. I declare under penalty of perjury that the foregoing is true and correct.

Angela C. Ni

EXHIBIT 1

US008598219B2

(12) **United States Patent**
Calderari et al.

(10) **Patent No.: US 8,598,219 B2**
(45) **Date of Patent: *Dec. 3, 2013**

(54) **LIQUID PHARMACEUTICAL FORMULATIONS OF PALONOSETRON**

(71) Applicants: **Helsinn Healthcare S.A.**, Lugano (CH); **Roche Palo Alto LLC**, Palo Alto, CA (US); **Simone Macciocchi**, Melide (CH); **Giulio Macciocchi**, Breganzona (CH)

(72) Inventors: **Giorgio Calderari**, Rancate (CH); **Daniele Bonadeo**, Casalzuigno (IT); **Roberta Cannella**, Varese (IT); **Alberto Macciocchi**, Melide (CH); **Andrew Miksztal**, Palo Alto, CA (US); **Thomas Malefyt**, Carmel Valley, CA (US); **Kathleen M Lee**, Palo Alto, CA (US); **Carmine Panuccio**, Casnate con Bernat (IT)

(73) Assignees: **Helsinn Healthcare SA**, Lugano/Pazzallo (CH); **Roche Palo Alto LLC**, Palo Alto, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **13/901,437**

(22) Filed: **May 23, 2013**

(65) **Prior Publication Data**

US 2013/0261592 A1 Oct. 3, 2013

Related U.S. Application Data

(63) Continuation-in-part of application No. 13/087,012, filed on Apr. 14, 2011, now Pat. No. 8,518,981, which is a continuation of application No. 11/186,311, filed on Jul. 21, 2005, now Pat. No. 7,947,724, which is a continuation of application No. PCT/EP2004/000888, filed on Jan. 30, 2004.

(60) Provisional application No. 60/444,351, filed on Jan. 30, 2003.

(51) **Int. Cl.**
A01N 43/52 (2006.01)

(52) **U.S. Cl.**
USPC **514/397**

(58) **Field of Classification Search**
USPC 514/397
See application file for complete search history.

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Primary Examiner — Shirley Gembeh
(74) *Attorney, Agent, or Firm* — Clark G. Sullivan; Troutman Sanders LLP

(57) **ABSTRACT**

The present invention relates to shelf-stable liquid formulations of palonosetron for reducing chemotherapy and radiotherapy induced emesis with palonosetron. The formulations are particularly useful in the preparation of intravenous and oral liquid medicaments.

8 Claims, No Drawings

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LIQUID PHARMACEUTICAL FORMULATIONS OF PALONOSETRON

FIELD OF THE INVENTION

The present invention relates to shelf-life stable liquid formulations of palonosetron that are especially useful in the preparation of injectable and oral medicaments.

BACKGROUND OF THE INVENTION

Emesis is a devastating consequence of cytotoxic therapy, radiotherapy, and post-operative environments that drastically affects the quality of life of people undergoing such treatments. In recent years a class of drugs referred to as 5-HT_3 (5-hydroxytryptamine) receptor antagonists has been developed that treat such emesis by antagonizing cerebral functions associated with the 5-HT_3 receptor. See *Drugs Acting on 5-Hydroxytryptamine Receptors*: The Lancet Sep. 23, 1989 and references cited therein. Drugs within this class include ondansetron, granisetron, alosetron, tropisetron, and dolasetron. These 5-HT_3 antagonists are often administered intravenously shortly before chemotherapy or radiotherapy is initiated, and can be administered more than once during a cycle of chemotherapy or radiotherapy. In addition, they are often supplied as tablets or oral elixirs to either supplement an intravenous administration, or to ease home usage of the drug if the patient is self-administering the chemotherapeutic regimen.

Because some chemotherapeutic agents can induce emesis over extended periods of several days even when they are administered only once, it would be desirable to administer an emesis-inhibiting drug such as a 5-HT_3 antagonist every day until the risk of emesis has substantially subsided. The present class of 5-HT_3 antagonists has not proven especially helpful meeting this need, however, because the 5-HT_3 receptor antagonists currently marketed have proven to be less effective in controlling delayed nausea and vomiting than they are at controlling acute emesis. Sabra, K, *Choice of a 5HT_3 Receptor Antagonist for the Hospital Formulary*. EHP, October 1996; 2 (suppl 1):S19-24.

Recently, clinical investigations have been made concerning palonosetron, a new 5-HT_3 receptor antagonist reported in U.S. Pat. No. 5,202,333. These investigations have shown that the drug is an order of magnitude more potent than most existing 5-HT_3 receptor antagonists, has a surprising half-life of about 40 hours, and is effective to reduce delayed-onset nausea induced by chemotherapeutic agents. However, formulating palonosetron in liquid formulations has not proven an easy task, typically due to shelf-stability issues. U.S. Pat. No. 5,202,333 discloses an intravenous formulation of palonosetron in example 13 that contains the following ingredients:

Ingredient	Mg
Palonosetron HCl	10-100 mg.
Dextrose Monohydrate	q.s. to make Isotonic
Citric Acid Monohydrate	1.05 mg.
Sodium Hydroxide	0.18 mg.
WFJ	To 1.0 ml.

The formulation has a pH of 3.7 and a shelf stability of less than the 1-2 year time period required by health authorities in various countries.

Ondansetron, its uses, and medicaments made with ondansetron are disclosed in U.S. Pat. Nos. 4,695,578, 4,753,789, 4,929,632, 5,240,954, 5,344,658, 5,578,628, 5,578,632, 5,922,749, 5,622,720, 5,955,488, and 6,063,802. Commercially it is distributed by GlaxoSmithKline as Zofran® and is indicated for prevention of postoperative nausea and vomiting (PONV), cancer chemotherapy-induced nausea and vomiting (CINV), and radiotherapy-induced nausea and vomiting (RINV) and it is available as an injection, tablets and solution, and as Zofran ODT® (ondansetron) Orally Disintegrating Tablets.

Granisetron, its uses, and medicaments made with granisetron are disclosed in U.S. Pat. Nos. 4,886,808, 4,937,247, 5,034,398 and 6,294,548. Commercially it is distributed by Roche Laboratories Inc. as Kytril®, indicated for the prevention of nausea and vomiting associated with chemotherapy or radiation therapy, and is offered in tablet form, oral solution, and as an injection.

Alosetron, its uses, and medicaments made with alosetron are disclosed in U.S. Pat. Nos. 5,360,800 and 6,284,770. Commercially it is distributed by GlaxoSmithKline as Lotronex®.

Tropisetron is commercially available as Navoban® (Novartis) CAS-89565-68-4 (tropisetron); CAS-105826-92-4 (tropisetron hydrochloride) and it is indicated for treatment of PONV and CINV.

Dolasetron, its uses, and medicaments made with ondansetron are disclosed in U.S. Pat. Nos. 5,011,846, and 4,906,755. Commercially it is distributed by Aventis Pharmaceuticals Inc. as Anzemet®, indicated for prevention of both PONV and CINV, and it is offered in the form of a tablet or an intravenous solution.

Therefore, there exists a need for a palonosetron formulation with increased stability and thereby increased shelf life. There also exists a need for an appropriate range of concentrations for both the 5-HT_3 receptor antagonist and its pharmaceutically acceptable carriers that would facilitate making a formulation with this increased stability.

It is an object of the present invention to provide a formulation of Palonosetron hydrochloride with increased pharmaceutical stability for preventing and/or reducing emesis.

It is another object of the invention to provide an acceptable range of concentrations which will stabilize a formulation containing Palonosetron hydrochloride.

It is a further object of the invention to provide a formulation of Palonosetron which would allow for prolonged storage.

It is also an object of the invention to provide a formulation of Palonosetron which would allow terminal sterilization.

SUMMARY OF THE INVENTION

The inventors have made a series of discoveries that support a surprisingly effective and versatile formulation for the treatment and prevention of emesis using palonosetron. These formulations are shelf stable for periods greater than 24 months at room temperature, and thus can be stored without refrigeration, and manufactured using non-aseptic, terminal sterilization processes.

In one aspect, the inventors have discovered that formulations which include the active ingredient palonosetron require in some instances only $1/10^{th}$ the amount of other previously known compounds for treating emesis, which surprisingly allows the use of concentrations of palonosetron far below those that would ordinarily be expected. Thus, in one embodiment the invention provides a pharmaceutically stable solution for preventing or reducing emesis comprising a) from

about 0.01 mg/mL to about 5 mg/mL palonosetron or a pharmaceutically acceptable salt thereof; and b) a pharmaceutically acceptable carrier.

The inventors have further discovered that by adjusting the formulation's pH and/or excipient concentrations it is possible to increase the stability of palonosetron formulations. Therefore, in another embodiment, the invention provides a pharmaceutically stable solution for preventing or reducing emesis comprising a) palonosetron or a pharmaceutically acceptable salt thereof; and b) a pharmaceutically acceptable carrier, at a pH from about 4.0 to about 6.0. In another embodiment the invention provides a pharmaceutically stable solution for preventing or reducing emesis comprising from about 0.01 to about 5.0 mg/ml palonosetron or a pharmaceutically acceptable salt thereof; from about 10 to about 100 millimoles citrate buffer; and from about 0.005 to about 1.0 mg/ml EDTA.

The inventors have further discovered that the addition of mannitol and a chelating agent can increase the stability of palonosetron formulations. Therefore, in still another embodiment the invention provides a pharmaceutically stable solution for preventing or reducing emesis comprising a) palonosetron or a pharmaceutically acceptable salt thereof and b) a pharmaceutically acceptable carrier, wherein the pharmaceutically acceptable carrier comprises a chelating agent and mannitol.

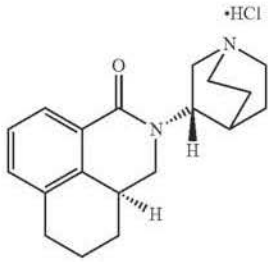
DETAILED DESCRIPTION OF THE INVENTION

Definitions

"Vial" means a small glass container sealed with the most suitable stopper and seal, other suitable primary containers may be used, for instance, but not limited to, pre-filled syringes. Vial also means a sealed container of medication that is used one time only, and includes breakable and non-breakable glass vials, breakable plastic vials, miniature screw-top jars, and any other type of container of a size capable of holding only one unit dose of palonosetron (typically about 5 mls.).

Throughout this specification the word "comprise," or variations such as "comprises" or "comprising," will be understood to imply the inclusion of a stated element, integer or step, or group of elements, integers or steps, but not the exclusion of any other element, integer or step, or group of elements, integers or steps

"Palonsetron" means (3aS)-2,3,3a,4,5,6-Hexahydro-2-[(S)-1-Azabicyclo[2.2.2]oct-3-yl]2,3,3a,4,5,6-hexahydro-1-oxo-1Hbenz[de]isoquinoline, and is preferably present as the monohydrochloride. Palonosetron monohydrochloride can be represented by the following chemical structure:



Concentrations—When concentrations of palonosetron are given herein, the concentration is measured in terms of the weight of the free base. Concentrations of all other ingredients are given based on the weight of ingredient added to the solution.

"Pharmaceutically acceptable" means that which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes that which is acceptable for veterinary use as well as human pharmaceutical use.

"Pharmaceutically acceptable salts" means salts which are pharmaceutically acceptable, as defined above, and which possess the desired pharmacological activity. Such salts include acid addition salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or with organic acids such as acetic acid, propionic acid, hexanoic acid, heptanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, o-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2,-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid p-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, p-toluenesulfonic acid, camphorsulfonicacid, 4-methylbicyclo[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like.

In addition, pharmaceutically acceptable salts may be formed when an acidic proton present is capable of reacting with inorganic or organic bases. Acceptable inorganic bases include sodium hydroxide, sodium carbonate, potassium hydroxide, aluminum hydroxide and calcium hydroxide. Acceptable organic bases include ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine and the like.

Discussion

The fact that palonosetron can be formulated in some instances at concentrations of only about $1/10^{th}$ the amount of other previously known compounds for treating emesis, surprisingly allows the use of concentrations of palonosetron far below those that would ordinarily be expected. Thus, in one embodiment the invention provides a pharmaceutically stable solution for preventing or reducing emesis comprising a) from about 0.01 mg/mL to about 5 mg/mL palonosetron or a pharmaceutically acceptable salt thereof; and b) a pharmaceutically acceptable carrier. Similarly, in another embodiment the invention provides a method of formulating a pharmaceutically stable solution of palonosetron comprising admixing from about 0.01 mg/mL to about 5 mg/mL palonosetron or a pharmaceutically acceptable salt thereof; with a pharmaceutically acceptable carrier. In alternative embodiments, the formulation includes palonosetron or a pharmaceutically acceptable salt thereof in a concentration from about 0.02 mg/mL to about 1.0 mg/mL, from about 0.03 mg/mL to about 0.2 mg/mL, and most optimally about 0.05 mg/ml.

A particular advantage associated with the lower dosages of intravenous palonosetron is the ability to administer the drug in a single intravenous bolus over a short, discrete time period. This time period generally extends from about 10 to about 60 seconds, or about 10 to about 40 seconds, and most preferably is about 10 to 30 seconds. In one particular embodiment the palonosetron is supplied in vials that comprise 5 ml. of solution, which equates to about 0.25 mg of palonosetron at a concentration of about 0.05 mg/ml.

The inventors have further discovered that by adjusting the formulation's pH and/or excipient concentrations it is possible to increase the stability of palonosetron formulations. Therefore, in another embodiment, the invention provides a pharmaceutically stable solution for preventing or reducing emesis comprising a) palonosetron or a pharmaceutically acceptable salt thereof; and b) a pharmaceutically acceptable carrier, at a pH from about 4.0 to about 6.0. Similarly, in another embodiment the invention provides a method of formulating a pharmaceutically stable solution of palonosetron comprising admixing a) palonosetron or a pharmaceutically acceptable salt thereof; and b) a pharmaceutically acceptable carrier, at a pH from about 4.0 to about 6.0. In alternative embodiments, the pH is from about 4.5 to about 5.5, and most optimally about 5.0. There are many examples to those of skill in the art of suitable solutions to adjust the pH of a formulation. Two exemplary solutions are sodium hydroxide and hydrochloric acid solution, either of which could be used to adjust the pH of the formulation.

In another embodiment the invention provides a pharmaceutically stable solution for preventing or reducing emesis comprising from about 0.01 to about 5.0 mg/ml palonosetron or a pharmaceutically acceptable salt thereof and (i) from about 10 to about 100 millimoles citrate buffer, and/or (ii) from about 0.005 to about 1.0 mg/ml EDTA. Similarly, in another embodiment the invention provides a method of formulating a pharmaceutically stable solution of palonosetron comprising admixing from about 0.01 to about 5.0 mg/ml palonosetron or a pharmaceutically acceptable salt thereof and (i) from about 10 to about 100 millimoles citrate buffer, and/or (ii) from about 0.005 to about 1.0 mg/ml EDTA. The citrate buffer can be in the form of citric acid and/or a salt of citric acid such as trisodium citrate. In various embodiments, the ranges of one or more of the foregoing ingredients can be modified as follows:

- The formulation may comprise palonosetron or a pharmaceutically acceptable salt thereof in a concentration from about 0.02 mg/mL to about 1.0 mg/mL, from about 0.03 mg/mL to about 0.2 mg/mL palonosetron hydrochloride, and most optimally about 0.05 mg/ml.
- The formulation may comprise citrate buffer in a concentration of from about 10 to about 40 millimoles, or 15-30 millimoles.
- The formulation may comprise EDTA in a concentration of from about 0.005 mg/ml to about 1.0 mg/ml, or about 0.3 to about 0.7 mg/ml, and most optimally about 0.5 mg/ml.

The inventors have further discovered that the addition of mannitol and a chelating agent can increase the stability of palonosetron formulations. Therefore, in still another embodiment the invention provides a pharmaceutically stable solution for preventing or reducing emesis comprising a) palonosetron or a pharmaceutically acceptable salt thereof and b) a pharmaceutically acceptable carrier, wherein the pharmaceutically acceptable carrier comprises a chelating agent and mannitol. Similarly, in another embodiment the invention provides a method of formulating a pharmaceutically stable solution of palonosetron comprising admixing a) palonosetron or a pharmaceutically acceptable salt thereof and b) a pharmaceutically acceptable carrier, wherein the pharmaceutically acceptable carrier comprises a chelating agent and mannitol. The chelating agent is preferably EDTA, and, in various embodiments the chelating agent is present in a concentration of from about 0.005 to about 1.0 mg/mL or from about 0.05 mg/mL to about 1.0 mg/mL or from about 0.3 to about 0.7 mg/ml, or most optimally about 0.5 mg/mL. In various embodiments the mannitol is present in a concentration of from about 10.0 mg/ml to about 80.0 mg/ml, from about 20.0 mg/mL to about 60.0 mg/ml, or from about 40.0 to about 45.0 mg/ml.

Injectable formulations are typically formulated as aqueous solutions in which water is the primary excipient. Oral formulations will differ from injectable formulations generally by the additional presence of flavoring agents, coloring agents, or viscosity agents. Natural or synthetic sweeteners include, among others, mannitol, sorbitol, saccharose, saccharine, aspartame, acelsulphame K, or cyclamate. These agents are generally present in concentrations in excess of 100 mg/ml or 250 mg/ml when used as sweetening agents, in contrast to the 41.5 mg/ml concentration of mannitol described in some of the embodiments of the invention, in which mannitol is acting simply as a tonicifying agent.

The formulations of the present invention are particularly suited for use in injectable and oral liquid formulations, but it will be understood that the solutions may have alternative uses. For example, they may be used as intermediates in the preparation of other pharmaceutical dosage forms. Similarly, they may have other routes of administration including intranasal or inhalation. Injectable formulations may take any route including intramuscular, intravenous or subcutaneous.

Still further embodiments relate to improvements in the ease with which the palonosetron formulation can be stored or manufactured. In particular, the inventors have discovered that the formulations of the present invention allow storage of the product for extended periods at room temperature. Thus, in yet another embodiment the invention provides a method of storing one or more containers in which are contained a solution of palonosetron or a pharmaceutically acceptable salt thereof comprising: a) providing a room comprising said one or more containers; b) adjusting or maintaining the temperature of the room at greater than about ten, 15, or 20 degrees celcius; and c) storing said containers in said room for one month, 3 months, 6 months, one year, 18 months, 24 months or more (but preferably not exceeding 36 months), wherein (i) the palonosetron or pharmaceutical salt thereof is present in a concentration of from about 0.01 mg/mL to about 5.0 mg/mL, (ii) the pH of the solution is from about 4.0 to about 6.0, (iii) the solution comprises from about 0.01 to about 5.0 mg/ml palonosetron or a pharmaceutically acceptable salt thereof, from about 10 to about 100 millimoles citrate buffer and from about 0.005 to about 1.0 mg/ml EDTA, (iv) the solution comprises a chelating agent, or (v) the solution comprises from about 10 to about 100 milliMoles of a citrate buffer.

The stability of the foregoing formulations also lends itself well to terminal sterilization processes in the manufacturing process. Therefore, in still another embodiment the invention provides a method of filling a container in which is contained a solution of palonosetron or a pharmaceutically acceptable salt thereof comprising: a) providing one or more sterile open containers (preferably 5 ml. vials); b) filling said containers with a solution of palonosetron in a non-aseptic environment; c) sealing said filled containers; and d) sterilizing said sealed, filled containers, wherein (i) the palonosetron or pharmaceutical salt thereof is present in a concentration of from about 0.01 mg/mL to about 5 mg/mL, (ii) the pH of the solution is from about 4.0 to about 6.0, (iii) the solution comprises from about 0.01 to about 5.0 mg/ml palonosetron or a pharmaceutically acceptable salt thereof, from about 10 to about 100 millimoles citrate buffer and from about 0.005 to about 1.0 mg/ml EDTA, (iv) the solution comprises a chelating agent, or (v) the solution comprises from about 10 to about 100 milliMoles of a citrate buffer.

EXAMPLES

Example 1

Stabilizing pH

A study was conducted to determine the effect of pH on formulations containing palonosetron hydrochloride, measuring the stability at 80° C. at pH 2.0, 5.0, 7.4, and 10.0. The results indicated that palonosetron hydrochloride is most stable at pH 5.0.

Example 2

Stabilizing Concentration Ranges

A formulation optimization study was performed using an experimental design software. Twenty-four lots of drug product were analyzed to investigate the appropriate concentration ranges for palonosetron hydrochloride (0.05 mg/mL to 5.0 mg/mL), citrate buffer (0 to 80 mM) and EDTA (0 to 0.10%). The level of EDTA and citrate buffer were selected based on the optimal formulation, which was shown to be formulated with EDTA 0.05% and 20 mM citrate buffer at pH 5.0. The results of this study indicated that palonosetron concentration was also a critical factor in chemical stability, with greatest stability seen at the lowest palonosetron concentrations.

Example 3

Tonicifying Agent

Formulations of palonosetron hydrochloride in citrate buffer were prepared including either a) sodium chloride or b) mannitol. The palonosetron hydrochloride formulation including mannitol showed superior stability. The optimum level of mannitol required for an isotonic solution was found to be 4.15%.

Example 4

Formulation I

The following is a representative pharmaceutical formulation containing palonosetron that is useful for intravenous formulations, or other liquid formulations of the drug.

Ingredient	mg/mL
Palonosetron Hydrochloride	0.05*
Mannitol	41.5
EDTA	0.5
Trisodium citrate	3.7
Citric acid	1.56
WFJ	q.s. to 1 ml
Sodium hydroxide solution and/or hydrochloric acid solution	pH 5.0 ± 0.5

*calculated as a free base

Example 5

Formulation II

The following is a representative pharmaceutical formulation containing palonosetron that is useful for oral formulations, or other liquid formulations of the drug.

Ingredient	mg/mL
Palonosetron Hydrochloride	0.05*
Mannitol	150
EDTA	0.5
Trisodium citrate	3.7
Citric acid	1.56
WFJ	q.s. to 1 ml
Sodium hydroxide solution and/or hydrochloric acid solution	pH 5.0 ± 0.5
Flavoring	q.s.

*calculated as a free base

Example 6

Stability of Palonosetron without Dexamethasone

The physical and chemical stability of palonosetron HCl was studies in concentrations of 5 μg/mL and 30 μg/mL in 5% dextrose injection, 0.9% sodium chloride injection, 5% dextrose in 0.45% sodium chloride injection, and dextrose 5% in lactated Ringer's injection. The admixtures were evaluated over 14 days at 4° C. in the dark and for 48 hours at 23° C. under fluorescent light.

Test samples of palonosetron HCl were prepared in polyvinyl chloride (PVC) bags of the infusion solutions at concentrations of 5 and 30 μg/mL. Evaluations for physical and chemical stability were performed on samples taken initially and after 1, 3, 5, 7, and 14 days of storage at 4° C. and after 1, 4, 24, and 48 hours at 23° C. Physical stability was assessed using visual observation in normal room light and using a high-intensity monodirectional light beam. In addition, turbidity and particle content were measured electronically. Chemical stability of the drug was evaluated by using a stability-indicating high performance liquid chromatographic (HPLC) analytical technique.

All samples were physically stable throughout the study. The solution remained clear, and little or no change in particulate burden and haze level were found. Additionally, little or no loss of palonosetron HCl occurred in any of the samples at either temperature throughout the entire study period.

Example 7

Stability of Palonosetron with Dexamethasone

The physical and chemical stability of palonosetron HCl 0.25 mg admixed with dexamethasone (as sodium phosphate) 10 mg or 20 mg in 5% dextrose injection or 0.9% sodium chloride injection in polyvinyl chloride (PVC) minibags, and also admixed with dexamethasone (as sodium phosphate) 3.3 mg in 5% dextrose injection or 0.9% sodium chloride injection in polypropylene syringes at 4° C. in the dark for 14 days and at 23° C. exposed to normal laboratory fluorescent light over 48 hours, was studied.

Test samples of palonosetron HCl 5 μg/mL with dexamethasone (as sodium phosphate) 0.2 mg/mL and also 0.4 mg/mL were prepared in polyvinyl chloride (PVC) minibags of each infusion solution. Additionally, palonosetron HCl 25 μg/mL with dexamethasone (as sodium phosphate) 0.33 mg/mL in each infusion solution were prepared as 10 mL of test solution in 20-mL polypropylene syringes. Evaluations for physical and chemical stability were performed on samples taken initially and after 1, 3, 7, and 14 days of storage at 4° C. and after 1, 4, 24, and 48 hours at 23° C. Physical stability was assessed using visual observation in normal

room light and using a high-intensity monodirectional light beam. In addition, turbidity and particle content were measured electronically. Chemical stability of the drug was evaluated by using a stability-indicating high performance liquid chromatographic (HPLC) analytical technique.

All samples were physically compatible throughout the study. The solutions remained clear, and little or no change in particulate burden and haze level were found. Additionally, little or no loss of palonosetron HCl and dexamethasone occurred in any of the samples at either temperature throughout the entire study period.

Example 8

Formulation III

The following is a representative pharmaceutical formulation and container closure for palonosetron that is useful for intravenous infusion formulations.

Ingredient	Amount (mg)
Palonosetron Hydrochloride	0.75[a]
Sodium Chloride	450.0
EDTA	2.5
Sodium citrate	18.5
Citric acid monohydrate	7.8
WFJ	q.s. to 50 mL
Sodium hydroxide solution and/or hydrochloric acid solution	pH 4.8 ± 0.5
Container closure system	plastic container[b] plus rubber stopper[c]

[a]Calculated based on the weight of free base
[b]Polyethylene multilayer film infusion bag.
[c]Isoprene rubber stopper.

This invention has been described with reference to its preferred embodiments. Variations and modifications of the invention will be obvious to those skilled in the art from the foregoing detailed description of the invention.

What is claimed is:

1. A pharmaceutical single-use, unit-dose formulation for intravenous administration to a human to reduce the likelihood of cancer chemotherapy-induced nausea and vomiting, comprising a 5 mL sterile aqueous isotonic solution, said solution comprising:

palonosetron hydrochloride in an amount of 0.25 mg based on the weight of its free base;

from 0.005 mg/mL to 1.0 mg/mL EDTA; and

from 10 mg/mL to 80 mg/mL mannitol,

wherein said formulation is stable at 24 months when stored at room temperature.

2. The pharmaceutical formulation of claim **1**, wherein said EDTA is in an amount of 0.5 mg/mL.

3. The pharmaceutical formulation of claim **1**, wherein said mannitol is in an amount of 41.5 mg/mL.

4. The pharmaceutical formulation of claim **1**, wherein said solution further comprises a citrate buffer.

5. The pharmaceutical formulation of claim **4**, wherein said citrate buffer is at a concentration of 20 millimolar.

6. The pharmaceutical formulation of claim **1**, wherein said solution is buffered at a pH of 5.0 ±0.5.

7. The pharmaceutical formulation of claim **1**, wherein said EDTA is in an amount of 0.5 mg/mL, wherein said mannitol is in an amount of 41.5 mg/mL, wherein said solution further comprises a citrate buffer at a concentration of 20 millimolar, and wherein said solution is buffered at a pH of 5.0 ±0.5.

8. A pharmaceutical single-use, unit-dose formulation for intravenous administration to a human to reduce the likelihood of cancer chemotherapy-induced nausea and vomiting, comprising a 5 mL sterile aqueous isotonic solution, said solution comprising:

palonosetron hydrochloride in an amount of 0.25 mg based on the weight of its free base;

from 0.005 mg/mL to 1.0 mg/mL EDTA; and

from 10 mg/mL to 80 mg/mL mannitol, wherein said formulation is stable at 18 months when stored at room temperature.

* * * * *

EXHIBIT 2

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

HELSINN HEALTHCARE S.A. and ROCHE PALO ALTO LLC.,	:	
Plaintiffs,	:	Civil Action No. 13-5815 (MLC)(DEA)
v.	:	
DR. REDDY'S LABORATORIES, LTD., DR. REDDY'S LABORATORIES, INC., SANDOZ INC., TEVA PHARMACEUTICALS USA, INC., and TEVA PHARMACEUTICAL INDUSTRIES, LTD.,	:	Hon. Mary L. Cooper, U.S.D.J. Hon. Douglas E. Arpert, U.S.M.J.
Defendants.	:	

DEFENDANTS' PROPOSED CLAIM TERMS FOR CONSTRUCTION

Michael E. Patunas
Mayra V. Tarantino
LITE DEPALMA GREENBERG, LLC
Two Gateway Center
Suite 1201
Newark, NJ 07102
(973) 623-3000
mpatunas@litedepalma.com
mtarantino@litedepalma.com

Of Counsel:
George C. Lombardi
Lynn MacDonald Ulrich
Julia M. Johnson
David Luger
WINSTON & STRAWN LLP
35 West Wacker Drive
Chicago, IL 60601
(312) 558-5600
glombardi@winston.com
lulrich@winston.com
jmjohnson@winston.com
dluger@winston.com

Jovial Wong
WINSTON & STRAWN LLP
1700 K Street
Washington, DC 20006
(202) 282-5000
jwong@winston.com

Attorneys for Defendants Teva Pharmaceuticals USA, Inc. and Teva Pharmaceutical Industries Ltd.

Eric I. Abraham
Christina Saveriano
HILL WALLACK LLP
202 Carnegie Center
Princeton, NJ 08540
(609) 924-0808
eabraham@hillwallack.com
csaverino@hillwallack.com

Of Counsel:
David Doyle
Elizabeth Cary Miller
MORRISON & FOERSTER LLP
12531 High Bluff Drive, Suite 1000
San Diego, CA 92130
(858) 720-5100
ddoyle@mofo.com
emiller@mofo.com

Matthew D'Amore
Jayson L. Cohen
Hui Liu
MORRISON & FOERSTER LLP
1290 Avenue of the Americas
New York, NY 10104-0050
(212) 468-8000
mdamore@mofo.com
jcohen@mofo.com
hliu@mofo.com

Attorneys for Defendant Sandoz Inc.

Stuart D. Sender
Michael H. Imbacuan
Stephanie L. Donahue
H. Howard Wang
BUDD LARNER, P.C.
150 John F. Kennedy Parkway
Short Hills, NJ 07078-0999
(973) 379-4800
ssender@buddlarner.com
mimbacuan@buddlarner.com
sdonahue@buddlarner.com
hwang@buddlarner.com

Attorneys for Defendants
Dr. Reddy's Laboratories, Ltd. and
Dr. Reddy's Laboratories, Inc.

Pursuant to the Court's March 4, 2014 Pretrial Scheduling Order, and the parties' subsequent agreement, Defendants Teva Pharmaceuticals USA, Inc. and Teva Pharmaceutical Industries Ltd. ("Teva"), Dr. Reddy's Laboratories, Ltd. and Dr. Reddy's Laboratories, Inc. ("DRL"), and Sandoz Inc. ("Sandoz") (collectively, "Defendants") hereby identify the following proposed terms to be construed for the asserted claims of U.S. Patent Nos. 8,518,981 (the "'981 patent"); 8,598,218 (the "'218 patent"); and 8,598,219 (the "'219 patent"). Defendants reserve the right to include additional terms or withdraw terms, and Defendants will continue to evaluate whether constructions of any terms are appropriate based on Plaintiffs' proposed terms and constructions.

Claim Term	Asserted Patents and Claims
"filling said containers"	Claim 1 of the '981 patent Claims 1 and 11 of the '218 patent
"A method of manufacturing and terminally sterilizing a finished single unit dose vial of palonosetron or a pharmaceutically acceptable salt thereof comprising"	Claim 1 of the '981 patent Claims 1 and 11 of the '218 patent
"A pharmaceutical single-use, unit-dose formulation for intravenous administration to a human to reduce the likelihood of cancer chemotherapy-induced nausea and vomiting comprising"	Claims 1 and 8 of the '219 patent
"pharmaceutically stable"	Claim 1 of the '981 patent Claims 1 and 11 of the '218 patent

By:

LITE DEPALMA GREENBERG, LLC

Attorneys for Defendants Teva Pharmaceuticals USA, Inc. and Teva Pharmaceutical Industries, Ltd.

By: */s/ Mayra V. Tarantino*
Michael E. Patunas
Mayra V. Tarantino
Two Gateway Center
Suite 1201
Newark, NJ 07102

Dated: May 5, 2014

HILL WALLACK LLP

Attorneys for Defendant Sandoz Inc.

By*: /s/ Eric I. Abraham*
Eric I. Abraham
202 Carnegie Center
Princeton, NJ 08540

Dated: May 5, 2014

BUDD LARNER, P.C.

Attorneys for Defendants Dr. Reddy's Laboratories, Ltd. and Dr. Reddy's Laboratories, Inc.

By: */s/ Michael H. Imbacuan*
Stuart D. Sender
Michael H. Imbacuan
Stephanie L. Donahue
H. Howard Wang
150 John F. Kennedy Parkway
Short Hills, NJ 07078-0999

Dated: May 5, 2014

EXHIBIT 3

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

HELSINN HEALTHCARE S.A. and ROCHE PALO ALTO LLC.,	:	
Plaintiffs,	:	
v.	:	Civil Action No. 13-5815 (MLC)(DEA)
DR. REDDY'S LABORATORIES, LTD., DR. REDDY'S LABORATORIES, INC., SANDOZ INC., TEVA PHARMACEUTICALS USA, INC., and TEVA PHARMACEUTICAL INDUSTRIES, LTD.,	:	Hon. Mary L. Cooper, U.S.D.J. Hon. Douglas E. Arpert, U.S.M.J.
Defendants.	:	

DEFENDANTS' PRELIMINARY CLAIM CONSTRUCTIONS

Michael E. Patunas
Mayra V. Tarantino
LITE DEPALMA GREENBERG, LLC
Two Gateway Center
Suite 1201
Newark, NJ 07102
(973) 623-3000
mpatunas@litedepalma.com
mtarantino@litedepalma.com

Of Counsel:
George C. Lombardi
Lynn MacDonald Ulrich
Julia M. Johnson
David Luger
WINSTON & STRAWN LLP
35 West Wacker Drive
Chicago, IL 60601
(312) 558-5600
glombardi@winston.com
lulrich@winston.com
jmjohnson@winston.com
dluger@winston.com

Jovial Wong
WINSTON & STRAWN LLP
1700 K Street
Washington, DC 20006
(202) 282-5000
jwong@winston.com

Attorneys for Defendants Teva Pharmaceuticals USA, Inc. and Teva Pharmaceutical Industries Ltd.

Eric I. Abraham
Christina Saveriano
HILL WALLACK LLP
202 Carnegie Center
Princeton, NJ 08540
(609) 924-0808
eabraham@hillwallack.com
csaverino@hillwallack.com

Of Counsel:
David Doyle
Elizabeth Cary Miller
MORRISON & FOERSTER LLP
12531 High Bluff Drive, Suite 1000
San Diego, CA 92130
(858) 720-5100
ddoyle@mofo.com
emiller@mofo.com

Matthew D'Amore
Jayson L. Cohen
Hui Liu
MORRISON & FOERSTER LLP
250 W. 55th Street
New York, NY 10019-9601
(212) 468-8000
mdamore@mofo.com
jcohen@mofo.com
hliu@mofo.com

Attorneys for Defendant Sandoz Inc.

Stuart D. Sender
Michael H. Imbacuan
Stephanie L. Donahue
H. Howard Wang
BUDD LARNER, P.C.
150 John F. Kennedy Parkway
Short Hills, NJ 07078-2703
(973) 379-4800
ssender@buddlarner.com
mimbacuan@buddlarner.com
sdonahue@buddlarner.com
hwang@buddlarner.com

Attorneys for Defendants
Dr. Reddy's Laboratories, Ltd. and
Dr. Reddy's Laboratories, Inc.

Pursuant to the Court's March 4, 2014 Pretrial Scheduling Order, and the parties subsequent agreement, Defendants Teva Pharmaceuticals USA, Inc. and Teva Pharmaceutical Industries Ltd. ("Teva"), Dr. Reddy's Laboratories, Ltd. and Dr. Reddy's Laboratories, Inc. ("DRL"), and Sandoz Inc. ("Sandoz") (collectively, "Defendants") hereby identify the following preliminary constructions for each of the proposed terms to be construed for the asserted claims of U.S. Patent Nos. 8,518,981 (the "'981 patent"); 8,598,218 (the "'218 patent"); and 8,598,219 (the "'219 patent"). Defendants further identify/designate all evidence that Defendants intend to rely upon to support the proposed constructions. Defendants reserve the right to include additional terms or withdraw terms, and Defendants will continue to evaluate whether constructions of any terms are appropriate based on Plaintiffs' proposed terms and constructions.

Claim Term	Preliminary Construction	Evidence
"filling said containers" Claim 1 of the '981 patent Claims 1 and 11 of the '218 patent	"filling said containers in a non-aseptic process"	The '981 patent, col. 1, line 10-col. 10, line 38; The '218 patent, col. 1, line 10-col. 10, line 47; U.S. Provisional Application No. 60/444,351; Application No. PCT/EP2004/000888; The prosecution history of U.S. Application No. 13/087,012 generally, including at least • Application filed 4/14/2011 • Preliminary Amendment dated 4/14/2011 • Declaration of Valentino J. Stella, Ph.D. dated 9/19/2007 • Declaration of Daniele Bonadeo dated 2/9/2009 • Supplemental Declaration

		of Daniele Bonadeo dated 6/8/2009 • Office Action dated 3/12/2012 • Amendment and Response dated 7/2/2012 • Office Action dated 7/19/2012 • Amendment and Response dated 7/26/2012 • Supplemental Amendment dated 12/26/2012 • Amendment Under 37 CFR 1.312 dated 3/20/2013 • Response to Rule 312 Communication dated 4/4/2013 • Amendment to Accompany RCE dated 5/23/2013 • Interview Summary dated 6/13/2013 • Applicant Summary of Examiner Interview dated 6/17/2013 • Reasons for Allowance dated 7/3/2013 • All references cited during prosecution The prosecution history of U.S. Application No. 13/901,288 generally, including at least • Application filed 5/23/2013 • Preliminary Amendment dated 5/23/2013 • Applicant Summary of Examiner Interview dated 6/17/2013 • Interview Summary dated 8/22/2013 • Reasons for Allowance dated 9/6/2013 • All references cited during prosecution

		Remington, The Science and Practice of Pharmacy, 20th ed. (2000), Chapters 40-42 and 52. Pharmaceutical Dosage Forms: Parenteral Medications, Volume 1, Ch. 4 (Kenneth E. Avis et al., ed.) (Marcel Dekker Inc. 2d ed. 1992).
"A method of manufacturing and terminally sterilizing a finished single unit dose vial of palonosetron or a pharmaceutically acceptable salt thereof comprising" Claim 1 of the '981 patent Claims 1 and 11 of the '218 patent	Defendants do not believe that this term is a limitation of the asserted claims. If the Court finds that this term is a limitation and should be construed, it should be construed as: "A method of manufacturing using non-aseptic processes and terminally sterilizing a finished single unit dose vial of palonosetron or a pharmaceutically acceptable salt thereof comprising"	*Am. Med. Sys. v. Biolitec, Inc.*, 618 F.3d 1354 (Fed. Cir. 2010); *Symantex Corp. v. Computer Assocs. Int'l, Inc.*, 522 F.3d 1279 (Fed. Cir. 2008); *Catalina Marketing Int'l v. Coolsavings.com*, 289 F.3d 801 (Fed. Cir. 2002); *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368 (Fed. Cir. 2001); *IMS Tech, Inc. v. Haas Automation, Inc.*, 206 F.3d 1422, (Fed. Cir. 2000); *STX LLC v. Brine, Inc.*, 211 F.3d 588 (Fed Cir. 2000); *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298 (Fed. Cir. 1999); *Rowe v. Dror*, 112 F.3d 473 (Fed. Cir. 1997). The '981 patent, col. 1, line 10-col. 10, line 38; The '218 patent, col. 1, line 10-col. 10, line 47; U.S. Provisional Application No. 60/444,351; Application No. PCT/EP2004/000888; The prosecution history of U.S. Application No. 13/087,012 generally, including at least • Application filed 4/14/2011 • Preliminary Amendment dated 4/14/2011 • Declaration of Valentino J.

		Stella, Ph.D. dated 9/19/2007 • Declaration of Daniele Bonadeo dated 2/9/2009 • Supplemental Declaration of Daniele Bonadeo dated 6/8/2009 • Office Action dated 3/12/2012 • Amendment and Response dated 7/2/2012 • Office Action dated 7/19/2012 • Amendment and Response dated 7/26/2012 • Supplemental Amendment dated 12/26/2012 • Amendment Under 37 CFR 1.312 dated 3/20/2013 • Response to Rule 312 Communication dated 4/4/2013 • Amendment to Accompany RCE dated 5/23/2013 • Interview Summary dated 6/13/2013 • Applicant Summary of Examiner Interview dated 6/17/2013 • Reasons for Allowance dated 7/3/2013 • All references cited during prosecution The prosecution history of U.S. Application No. 13/901,288 generally, including at least • Application filed 5/23/2013 • Preliminary Amendment dated 5/23/2013 • Applicant Summary of Examiner Interview dated 6/17/2013 • Interview Summary dated 8/22/2013

		• Reasons for Allowance dated 9/6/2013 • All references cited during prosecution Remington, The Science and Practice of Pharmacy, 20th ed. (2000), Chapters 40-42 and 52. Pharmaceutical Dosage Forms: Parenteral Medications, Volume 1, Ch. 4 (Kenneth E. Avis et al., ed.) (Marcel Dekker Inc. 2d ed. 1992).
"A pharmaceutical single-use, unit-dose formulation for intravenous administration to a human to reduce the likelihood of cancer chemotherapy-induced nausea and vomiting comprising" Claims 1 and 8 of the '219 patent	Defendants do not believe that this term is a limitation of the asserted claims. If the Court finds that this term is a limitation and should be construed, it should be construed as: "A pharmaceutical single-use, unit-dose formulation comprising"	*Am. Med. Sys. v. Biolitec, Inc.*, 618 F.3d 1354 (Fed. Cir. 2010); *Symantex Corp. v. Computer Assocs. Int'l, Inc.*, 522 F.3d 1279 (Fed. Cir. 2008); *Catalina Marketing Int'l v. Coolsavings.com*, 289 F.3d 801 (Fed. Cir. 2002); *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368 (Fed. Cir. 2001); *IMS Tech, Inc. v. Haas Automation, Inc.*, 206 F.3d 1422, (Fed. Cir. 2000); *STX LLC v. Brine, Inc.*, 211 F.3d 588 (Fed Cir. 2000); *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298 (Fed. Cir. 1999); *Rowe v. Dror*, 112 F.3d 473 (Fed. Cir. 1997). The '219 patent, col. 1, line 10-col. 10, line 38; U.S. Provisional Application No. 60/444,351; Application No. PCT/EP2004/000888; The prosecution history of U.S. Application No. 11/186,311 generally;

		The prosecution history of U.S. Application No. 11/388,268 generally; The prosecution history of U.S. Application No. 11/388,269 generally; The prosecution history of U.S. Application No. 11/388,270 generally; The prosecution history of U.S. Application No. 13/087,012 generally, including at least • Application filed 4/14/2011 • Preliminary Amendment dated 4/14/2011 • Declaration of Valentino J. Stella, Ph.D. dated 9/19/2007 • Declaration of Daniele Bonadeo dated 2/9/2009 • Supplemental Declaration of Daniele Bonadeo dated 6/8/2009 • Office Action dated 3/12/2012 • Amendment and Response dated 7/2/2012 • Office Action dated 7/19/2012 • Amendment and Response dated 7/26/2012 • Supplemental Amendment dated 12/26/2012 • Amendment Under 37 CFR 1.312 dated 3/20/2013 • Response to Rule 312 Communication dated 4/4/2013 • Amendment to Accompany RCE dated 5/23/2013 • Interview Summary dated 6/13/2013

		• Applicant Summary of Examiner Interview dated 6/17/2013 • Reasons for Allowance dated 7/3/2013 • All references cited during prosecution The prosecution history of U.S. Application No. 13/901,288 generally, including at least • Application filed 5/23/2013 • Preliminary Amendment dated 5/23/2013 • Applicant Summary of Examiner Interview dated 6/17/2013 • Interview Summary dated 8/22/2013 • Reasons for Allowance dated 9/6/2013 • All references cited during prosecution The prosecution history of U.S. Application No. 13/901,437 generally, including at least • Application filed 5/23/2013 • Applicant Summary of Examiner Interview dated 6/17/2013 • Interview Summary dated 7/11/2013 • Office Action dated 7/12/2013 • Interview Summary dated 7/22/2013 • Office Action dated 7/24/2013 • Office Action dated 7/29/2013 • Amendment and Response dated 7/30/2013 • Interview Summary dated 9/30/2013

		• Reasons for Allowance dated 9/30/2013 • All references cited during prosecution
"pharmaceutically stable" Claim 1 of the '981 patent Claims 1 and 11 of the '218 patent	"without significant change in chemical or physical integrity for pharmaceutical use"	The '981 patent, col. 1, line 10-col. 10, line 38; The '218 patent, col. 1, line 10-col. 10, line 47; U.S. Provisional Application No. 60/444,351; Application No. PCT/EP2004/000888; The prosecution history of U.S. Application No. 11/186,311 generally; The prosecution history of U.S. Application No. 11/388,268 generally; The prosecution history of U.S. Application No. 11/388,269 generally; The prosecution history of U.S. Application No. 11/388,270 generally; The prosecution history of U.S. Application No. 13/087,012 generally, including at least • Application filed 4/14/2011 • Preliminary Amendment dated 4/14/2011 • Declaration of Valentino J. Stella, Ph.D. dated 9/19/2007 • Declaration of Daniele Bonadeo dated 2/9/2009 • Supplemental Declaration of Daniele Bonadeo dated

		6/8/2009 • Office Action dated 3/12/2012 • Amendment and Response dated 7/2/2012 • Office Action dated 7/19/2012 • Amendment and Response dated 7/26/2012 • Supplemental Amendment dated 12/26/2012 • Amendment Under 37 CFR 1.312 dated 3/20/2013 • Response to Rule 312 Communication dated 4/4/2013 • Amendment to Accompany RCE dated 5/23/2013 • Interview Summary dated 6/13/2013 • Applicant Summary of Examiner Interview dated 6/17/2013 • Reasons for Allowance dated 7/3/2013 • All references cited during prosecution The prosecution history of U.S. Application No. 13/901,288 generally, including at least • Application filed 5/23/2013 • Preliminary Amendment dated 5/23/2013 • Applicant Summary of Examiner Interview dated 6/17/2013 • Interview Summary dated 8/22/2013 • Reasons for Allowance dated 9/6/2013 • All references cited during prosecution The United States Pharmacopeia

		USP 25, General Information, <1151> Pharmaceutical Dosage Forms (2002); Guidance for Industry, Q1A (R2) Stability Testing of New Drug Substances and Products, USFDA, 2003 (Revision 2); ICH Harmonised Tripartite Guideline, Stability Testing of New Drug Substances and Products Q1A (R2)(2003); ICH Harmonised Tripartite Guideline, Stability Testing of New Drug Substances and Products Q1A (1993); P. P. DeLuca and J.C. Boylan, Formulation of Small Volume Parenterals, in Pharmaceutical Dosage Forms: Parenteral Medications, Volume 1, Chapter 5, 173-248 (Kenneth E. Avis et al. eds., Marcel Dekker Inc., 2d ed. 1992). Remington, The Science and Practice of Pharmacy, 20th ed. (2000), Chapters 41, 42 and 52. The parties' claim construction briefing and related materials in Case No. 3:11-03962 concerning "pharmaceutically stable."[1]

[1] Defendants are amenable to construing this term at trial rather than briefing this term for a second time, as per the Court's guidance in Case No. 3:11-03962.

By:

LITE DEPALMA GREENBERG, LLC

Attorneys for Defendants Teva Pharmaceuticals USA, Inc. and Teva Pharmaceutical Industries, Ltd.

By: */s/ Mayra V. Tarantino*
Michael E. Patunas
Mayra V. Tarantino
Two Gateway Center
Suite 1201
Newark, NJ 07102

Dated: May 12, 2014

HILL WALLACK LLP

Attorneys for Defendant Sandoz Inc.

By*: /s/ Eric I. Abraham*
Eric I. Abraham
Christina Saveriano
202 Carnegie Center
Princeton, NJ 08540

Dated: May 12, 2014

BUDD LARNER, P.C.

Attorneys for Defendants Dr. Reddy's Laboratories, Ltd. and Dr. Reddy's Laboratories, Inc.

By: */s/ Michael H. Imbacuan*
Stuart D. Sender
Michael H. Imbacuan
Stephanie L. Donahue
H. Howard Wang
150 John F. Kennedy Parkway
Short Hills, NJ 07078-2703

Dated: May 12, 2014